TUBERCULOSIS OF THE BLADDER.

BY GEORGE WALKER, M.D.,

OF BALTIMORE.

Associate in Surgery, Johns Hopkins University.

In the preparation of the following article I have studied 413 cases of tuberculosis of the bladder which I have collected from the literature, and 34 others from Dr. Halsted's wards in the Johns Hopkins Hospital and my private practice. I have examined the preserved tissues from cases of bladder tuberculosis, and have gone over all of the records pertaining thereto in the Johns Hopkins Pathological Laboratory. By the kindness of Dr. Cullen I have been permitted to study additional material from Dr. Kelly's gynæcological service. I have also obtained specimens of this disease which have been preserved in other institutions; and in order to observe more fully its beginning and course I have inoculated the genito-urinary organs of guinea-pigs and rabbits, and watched as far as possible the development of the morbid process.

The literature of this subject is very voluminous, and the conclusions as to the surgical treatment are various and contradictory, rendering it difficult to arrive at the truth. The general impressions, however, which I have obtained from this perusal, in conjunction with my personal experience, have led me to the conclusions set forth in this paper.

HISTORY.

Prior to the fifteenth century there are no descriptions of disease of the bladder sufficiently clear to enable one to identify instances of vesical tuberculosis. And indeed, up to the writings of Ambroise Paré there are no records of this disease. After him there is no mention made of it until Bayle cited a number of cases of genito-urinary tuberculosis, and concluded that the process might be limited to the bladder, or at least not extend beyond the genito-urinary organs.

Læennec in 1819, in his exhaustive clinical and pathological study of general tuberculosis, found in several subjects that the disease was localized in the genito-urinary organs, and in the description of these cases he gave a very precise autopsy picture of tuberculosis of the bladder. Following him, John Howship in 1823 and Larcher in 1827 described this malady in some detail, the latter being the first to note the presence of tubercles in the vesical mucous membrane.

Cruveilhier, in his characteristically thorough manner, studied several examples of this affection, and was of the opinion that next after the kidney the bladder most frequently became implicated. No notice was taken of this observation until recently when it has been proved to be correct.

Rayer in 1841 made very accurate and beautiful drawings of various tuberculous lesions of the bladder and kidneys; several of these remain unsurpassed in clearness.

After a thorough study of a large number of cases, Wilkes in 1859 concluded that the bladder was never the primary seat, disease of the kidney always preceding its implication. Gebhard, in his admirable thesis, concurred in this opinion. Guyon and Lancereaux a few years later, on the other hand, expressed the opinion that the bladder was in most instances primarily affected, and that the kidneys were implicated by ascension. The profession seems to have been influenced largely by these teachings and to have generally adopted this view. Gradually, however, these ideas lost ground, and it is now known that the bladder is almost never the primary seat of tuberculosis. Moreover, the work of Cayle, Baumgarten, and others has proved that the disease rarely ascends to the kidney.

FREQUENCY OF BLADDER TUBERCULOSIS.

In 2390 general autopsies in the Johns Hopkins Hospital Pathological Laboratory, tuberculosis of some organ was found 710 times; in this number one or more of the genito-urinary organs was involved 160 times; the bladder was affected 22 times, but in no case was the disease primary in this viscus. The kidneys were affected 131 times (in 111 with miliary and in 20 with chronic tuberculosis), the prostate 17 times; the Fallopian tubes 16 times; the uterus 11 times; the epididymes or testes 9 times; the ureters 9 times; the urethra 4 times; the ovaries thrice; and the vagina twice.

Saxtorph in 10,016 autopsies found 547 instances of tuberculosis of the genito-urinary organs. There were 342 instances of acute miliary processes in the kidney, but only 4 of miliary tubercles in the bladder. In 205 cases of chronic genito-urinary tuberculosis, the bladder was involved *alone* only once, but in 52 cases there was a secondary implication of it—in 38 men (622 autopsies) and 14 women (3,894 autopsies). In the 38 men the kidney was implicated 32 times, the prostate 29 times, and the seminal vesicles 20 times. In the 14 women, the kidney was tuberculous 13 times; and the genital organs 3 times.

Von Groenow in 82 deaths from general tuberculosis found 14 invasions of the genito-urinary organs, among which there were 10 bladder implications. Posner in 115 tuberculous kidneys recorded 12 infections of the bladder (autopsy report). Heiberg in 16 instances of primary genito-urinary tuberculosis in the male observed implication of the bladder 11 times. In 13 cases of primary tuberculosis in the female, the bladder was implicated 8 times. In 32 instances of secondary infection of the genito-urinary tract in the male, the bladder was affected 9 times. In 22 in the female, 9 times. In the male series, there was no instance of an isolated bladder tuberculosis; in the female there was 1. Matile, in 1726 autopsies for tuberculosis, found that the genito-urinary tract had been invaded 123 times; among this number in 19 the bladder was tuberculous.

In 31 cases of genito-urinary tuberculosis noted by Goldberg the bladder was implicated in 23. There were 35 bladder infections in 51 cases of renal tuberculosis studied by Gaultier. Jullien, after a careful examination of 41 instances of tuberculosis of the prostate, records implication of the bladder in 13. Extension to the bladder was discovered by Desnos thirteen times in 16 cases of tuberculosis of the prostate. In 23 cases in which Israel operated for tuberculosis of the kidney the bladder had become infected in 11. Among 23 patients suffering from genito-urinary tuberculosis whose cases were recorded by Krzywicki, there were 13 who had bladder lesions.

PATHOLOGY.

The latest and by far the most comprehensive work which has been done on the pathology of tuberculosis of the bladder is by Motz and Hallé. I have adopted in part their classification and have not hesitated to draw largely on their descriptions.

We shall divide, somewhat arbitrarily I admit, tuberculosis of the bladder into the four following stages:

(1) The period of invasion and formation of tubercles.
(2) The period of superficial ulceration.
(3) The period of deeper infiltration.
(4) The period of more widespread destruction.

It is impossible to strike the boundary lines between these periods, for in some bladders they are so merged one into the other that nothing definite can be made out in regard to the stage. The third, that of infiltration, is usually the last, for the fourth, the period of destruction, occurs only seldom.

(1) Stage of Invasion.—It is rare that one has the opportunity of observing the very beginning of tuberculosis of the bladder. I have chanced on it once in a case of infection coming from the prostate.

The tubercles (according to Hallé and Motz) are usually situated in the lower half around the orifices of the ureters or in the trigone; they vary in size, from the smallest ones which are scarcely visible, up to that of a mustard seed. At first they are gray, transparent or hyaline, sometimes resembling minute cysts; others do not show this transparency, but are opaque from the onset; as they become older they assume a yellowish tinge. Both the yellow and the gray tubercles project slightly from the surface, each being surrounded by a faint rosy zone which is made up of injected blood vessels. The epithelial layer over them in the earliest stage is intact, but gradually loses its lustre, begins to exfoliate and later becomes necrotic. As the age of the tubercle advances there is a loss of substance at the apex and the formation of an extremely minute ulcer. This last picture is very seldom seen, for usually there is a coalescence of several tubercles before the ulcer is formed.

Following very closely the above described process, there can be made out a number of other tubercles springing up very close to the older ones, which in a short time merge with them, and form a conglomerate mass the size of a pea. This appears as an opaque projecting nodule which is covered with an intact lustreless and partly necrotic mucous membrane. This stage is the immediate predecessor of the ulcer.

Histologically, the tubercle appears to develop in the capillary zone just beneath the epithelium, and just above the derma. This situation was interpreted by Clado as meaning that the infection of the bladder was through the blood, and was not a direct contamination from the urine. Such a belief, however, is contrary to clinical observation and to many pathological facts. The development, therefore, of tubercles in this region, is probably explained by the entrance of the tubercle bacilli to the deeper layers through a small crack or fissure or by direct penetration.

The very first change which the presence of tubercle bacilli brings about is a slight dilatation of the minute blood vessels; immediately following this there is a proliferation of the connective tissue which gives rise to the formation of lymphoid cells; these at first are scattered, but they soon become more or less aggregated, and in the centre of such cell masses the epithelioid type appears. As the stage advances, by the use of careful staining methods, a change can be made out in both the epithelioid and lymphoid cell; the former presents a more granular protoplasm with a less vesicular nucleus, whereas the nucleus of the latter is much more deeply stained. Just at this time one or more typical giant cells are visible, and an invasion of leukocytes occurs. The cells in the centre soon begin to show more and more signs of degeneration until, finally, actual necrosis takes place and a microscopic cheesy mass is formed. The overlying mucous membrane at this time presents definite alterations, the blood vessels are slightly engorged, the epithelial cells have a granular protoplasm and a less clearly defined nucleus, and soon begin to exfoliate. The endothelium of the blood vessels immediately surrounding the tubercle proliferates, causing a thickening of the wall and occasionally occlusion of the lumen. The bacilli at first are more or less evenly distributed throughout the cell aggregation, but later they tend to disappear from the centre and are seen only in the periphery.

(2) Stage of Ulceration.—Occasionally one observes a necrosis of a single microscopic tubercle with the formation of an extremely minute ulcer; as a rule, however, several tubercles coalesce, necrose and slough, thus forming a much larger ulcerated area. The latter is usually the type which is first discovered and which marks the beginning of the stage of ulceration. The ulcer spreads itself irregularly in the surrounding mucous membrane, partly by the springing up and secondary necrosis of tubercles in its border, and partly by the erosion of the walls due to the tuberculous toxins.

As seen in this stage, then, the ulcerated area will measure from 2 to 5 mm. in its widest part; it is very irregular in shape, with small arms, which project into the surrounding tissue, and edges that are ragged, worm-eaten, and overhanging, or in other words, undermined; the base is covered by a very delicate anæmic granulation tissue, over which is irregularly spread a fibrinous exudate. The tissue immediately surrounding the edges is somewhat swollen, slightly indurated, and irregularly reddened. Lying in this red zone or outside of it, one can usually discover gray and yellow tubercles, which are irregularly scattered, or may form a definite ring. Two or three ulcers with their adjacent tubercles can generally be found in the same bladder; these may merge into each other, or an intact strip of mucous membrane may be left between them. Occasionally they are single, as reported by Broca, Clado, Coplin, Kümmel, Strauss, Battle, Fenwick and Burckhardt.

The ulcer, as a rule, involves the submucosa, but does not usually penetrate to the muscle; more rarely it completely erodes the submucosa and exposes the muscle, forming what is called a trabeculated ulcer; in still rarer instances it penetrates the entire muscular coat.

On histological examination, one sees that the surface of such an ulcer is covered by a thin layer of necrotic fibrin, immediately below which is tissue made up of small round cells, leukocytes, epithelioid cells, fibrinous masses, and dilated blood vessels, together with scattered cell aggregations showing a tubercular arrangement. The walls of the blood vessels show varying degrees of endothelial proliferation. In the lower layers of the ulcer, as the muscle is approached, there is an extensive round-celled infiltration, but no tubercles. Throughout this granulation tissue, tubercle bacilli are present; they are arranged in clumps, irregularly scattered among the cells with a tendency to aggregation in and around the tubercles.

Trabeculated Ulcer.—The active ulcer after eroding the submucous tissues lays bare the fibres of the muscle which in turn form its base; these being covered by only a thin layer of granulation tissue give rise to the formation of an uneven trabeculated surface. The edges of such an ulcer do not differ from those of the type first described, except that they are thicker, more ragged, and slightly more overhanging.

This type of ulceration occasionally continues to erode the muscle, and as a result ragged muscle fibres are seen projecting from the base.

Histologically the granulation base is formed of lymphoid cells, polymorphonuclear leukocytes, dilated blood vessels with an occasional attempt at the formation of cell aggregations resembling tubercles, but not usually developing into one definitely visible. The muscle itself is infiltrated with small round cells; this invasion is usually limited to the muscle immediately surrounding the base of the ulcer, but sometimes is much more extensive.

Granulation or Vegetating Ulcer.—Projecting from the sides and base of this type of ulcer are vegetations in the form of a dark velvety fringe or definite papillomatous masses. The larger of these projections are irregular in shape and occasionally are pedunculated as a result of the erosion which has occurred on their sides. The base of such an ulcer shows only a small amount of necrotic fibrin, and the edges are not so much undermined as is usual in other forms. This variety is infrequent, and when found has resulted from a very chronic kind of tuberculosis which is neither virulent nor progressive.

Histologically these vegetations present the cellular arrangement of ordinary non-tuberculous granulation tissue; some of the larger ones contain epithelioid and giant cells, an indication that they have been invaded by tuberculosis. The tubercle bacilli are not present in those which are made up only of granulation tissue.

Another and still rarer type is seen when the muscle has become eroded; here the projecting masses contain bits of muscle as well as granulation tissue.

The muscle in the stage of ulceration is always hypertrophied from the overwork caused by frequent micturition.

(3) STAGE OF INFILTRATION.—As the ulceration increases and penetrates nearly to, or into, the already thickened muscle, the tuberculous process, either directly or by its toxins, sets up in it an inflammatory reaction which is evidenced by the widespread infiltration with lymphoid cells and leukocytes, which in turn give rise to a subsequent development of fibrous tissue. Some specimens show only such an inflammatory change; in others there is a general dissemination of the tubercle bacilli, with a consequent formation of tubercles scattered throughout the tissue. The muscle which was hypertrophied before, now becomes much more thickened by this infiltration, more irritable, and consequently more responsive to stimulation; as a result there ensues an exaggeration in the frequency of micturition. As this stage progresses, there is a degeneration of the muscle, and a replacement of it by connective tissue, which gradually interferes with its contractile power, so that the bladder becomes unable to empty itself.

The ulceration in this stage of infiltration advances and finally becomes so extensive that there is almost complete erosion of the whole mucous membrane. In one case that I have observed, the mucosa was so nearly destroyed that there remained only small fragments here and there. Fenwick observed a bladder in the infiltration stage in which all the mucous membrane was exfoliated except the trigone. Kidd, in a similar bladder, found the inside lining a mass of granulation tissue, except over a small portion of the right lateral wall. Krzywicki records an example in which entire destruction of the whole mucous membrane and extensive invasion of the muscle were noted. In an exceptional instance, reported by Haeffner, half of the bladder mucous membrane was necrotic, although the muscle was not infiltrated nor the bladder contracted. In a specimen shown to me in the Baltimore City Hospital by Dr. Rohrer, there were only a few islands of mucous membrane left, and the muscle was nearly everywhere exposed and extensively thickened by infiltration and hypertrophy.

The wall of a bladder in the stage of infiltration is always thickened, sometimes enormously so, and the whole organ is very much reduced in size, so that its capacity ranges from 100 cc. to 20 cc. Immediately surrounding the outside of the bladder there is formed a somewhat thick layer of inflammatory tissue.

The histological structure of the ulcerating surface and of the muscle in the above condition has already been described.

Caseous Massive Infiltration.—This is a rare variety of the stage of infiltration. For its production two factors are necessary: First, very virulent micro-organisms, and secondly, a very feeble resistance on the part of the tissues. In this form there is a very diffuse spreading out of the tuberculous process on the surface of the bladder and a rapid invasion of the muscular coat with widespread caseous degeneration. The mucous lining of the bladder is covered with grayish-yellow caseous masses which project and render the surface uneven; hanging here and there from these masses and the mucosa are detached flakes of necrotic fibrin. There are few or no ulcerations. The muscle wall has been changed over a considerable extent into cheesy material, and what remains has undergone a partial disintegration. This wholesale destruction of the muscle has deprived the bladder of its tone and its power to contract, so that it is usually found distended; exceptionally it appears half contracted with rigid walls. The connective tissue outside of the muscle is rarely invaded.

Histologically there are large masses of grayish-yellow, entirely structureless material; around these areas in the still vital tissue are numerous rapidly necrosing tubercles. The muscle which remains is filled with small round cells, the individual fibres are slightly shrunken, the protoplasm of the muscle cells is granular, and the nuclei show a beginning fragmentation. Here and there one can see the outlines of single fibres surrounded by degenerated tissue, giving one the impression that the connective-tissue framework of the muscle has remained while the actual cell has vanished. Tubercle bacilli are present in enormous numbers, and frequently other organisms, particularly streptococci, have aided the work of destruction.

Diphtheroid Form.— This is a variety which is difficult to classify, but more nearly conforms to the infiltrative type than to the other processes. In this there are virulent tubercle bacilli, to which are added streptococci, or a very active form of the colon bacillus. The picture is that of an acute process, and shows an extremely rapid and extensive invasion of the mucous membrane and the muscle, which gives rise to the formation of an enormous yellowish-gray fibrinous exudate. Such a bladder has no unchanged mucous membrane; in fact, it is entirely covered by this dirty gray material, which forms a thick fluffy coat of various hues due to the different stages of necrosis. This fibrinous exudate is very intimately connected with the underlying mucous membrane and when separated from it leaves a bleeding surface. There are no ulcerations. Dittel and several others have reported such a condition of the bladder.

Histologically there is a very extensive inflammatory reaction, as shown by a general lymphoid and leukocytic infiltration, an enormous production of fresh tubercles and extensive localized areas of necrosis, but an almost complete absence of large masses of cheesy degeneration as seen in the massive type. The picture, therefore, resembles more closely that of a streptococcus inflammation, to which has been added the formation of the multiple tubercles. The exudate is made up of coagulated and necrotic fibrin and resembles somewhat that seen in diphtheria.

(4) STAGE OF DESTRUCTION.—In this stage the muscular coat has been more or less completely destroyed by a rather slow chronic type of tuberculosis and has been eroded, its place being taken by a granulating membrane. The bladder has lost its contractile power and has been converted into a distended flaccid bag. Throughout this newly formed tissue the tuberculous processes may or may not be present; there are usually no active lesions and occasionally the tuberculosis has entirely disappeared. Motz and Hallé have observed and very carefully described several such instances.

Heiler found at autopsy so complete a destruction of the bladder that it was difficult to find any remnants of it; in its place was a small granulating sac, with a fistula into the vagina, through which the urine continually dribbled.

Varieties.—Casper speaks of instances in which tubercle bacilli sometimes spread over the mucous membrane very quickly and produce a picture of an acute process not unlike a true cystitis. He terms the process a tuberculous cystitis, in contradistinction to a tuberculosis of the bladder. Such a differentiation is not needed and tends to confuse rather than to elucidate. A cystitis of this kind is rarely, if ever, the product of tubercle bacilli, but is usually due to the invasion of pyogenic organisms.

Bryson has made the unique observation of what he calls a localized parenchymatous tuberculous cystitis. He observed in a male on the anterior wall of the bladder a spiral-shaped spot the size of a silver dollar, which presented over its surface dark spots, but an intact epithelium; the remaining mucous membrane appeared normal. At first he did not understand its nature, but later, after finding tubercle bacilli, he decided that it was a rare type of a tuberculous lesion.

Stoeckel reports a very interesting condition which showed a number of polypoid excrescences; these appeared as raised pale areas, most of which were transparent; others were simple œdematous spots; and a few were grayish red. The trigone was normal except that it was very strongly injected; the bladder mucous membrane was entirely free from tubercles and ulcerations; no tubercle bacilli were to be found in the urine; but an inoculation of a guinea-pig was positive, thus proving that the process was tuberculous. I have seen a similar picture in a male, which was undoubtedly not tuberculous, but was due to the effects of an irritating substance in the urine. It seems to me, therefore, that Stoeckel's case might have been an instance of tuberculosis of the kidney, the bladder lesions being caused simply by irritating toxins. In another case, Stoeckel found definite tuberculosis of the bladder, which from time to time almost entirely disappeared, and then returned.

Mirabeau records the case of a female in whom he observed, some time before death, an ulcer in the bladder, but at the time of observation he was not able to discover any other tuberculous lesion. This ulcer was watched by cystoscopic examination and observed to heal; moreover, there was a complete subsidence of the symptoms for one year; although in the bladder, during this time, different spots of inflammation could be made out. One and a half years, presumably, according to his report, after the healing of the ulcer, the patient developed tuberculosis of the lungs and died. A second patient had several attacks of what appeared to be, from cystoscopic examination, inflammation of the bladder, but was proved to be tuberculous by the finding of tubercle bacilli in the urine; in the interval the symptoms became quiescent and the lesions in the bladder cleared up. Such an observation tends to confirm the idea of Casper. In a third instance, along with active ulcers, were found old scars which Mirabeau took to be healed foci.

Pericystitis.—In the later stages the bacilli themselves, or their toxins, probably the latter, get into the tissues immediately outside of the bladder and set up an adhesive inflammatory reaction; this produces a matting together of the bladder with the rectum, small intestines, etc. Englisch has observed and very carefully described this condition. This process does not usually show definite tubercles except in the last stage.

Mixed Infections.—I cannot state with any degree of exactness the percentage of the cases in which a secondary infection occurred, for the reason that in the majority of the reports no mention was made of the presence or absence of other organisms. In those which I have personally examined, pyogenic bacteria were absent from bladders which had not been catheterized, and present in those in which the catheter had been used. I do not mean that all infections are brought about in this manner, for there are innumerable instances in which a secondary invasion has been present without any instrumental interference. The pathological picture presented in a mixed infection differs slightly with the type of the organisms, but the picture is usually that of a tuberculous process with the addition of an ordinary inflammation. Some pyogenic organisms stimulate the activity of the tubercle bacilli; others have no effect upon them and a few are believed to even retard their growth. The organisms which have been found are colon bacilli, streptococci, staphylocci, gonococci and the proteus group. Streptococci and staphylococci, particularly the former, tend to increase the activity of the tubercle bacilli; colon bacilli do not aid their growth but produce a definite cystitis and in this way aggravate the symptoms; the proteus group sets up an ammoniacal fermentation which very greatly increases the pain and burning in urination, but possibly lessens the activity of the tubercle bacilli. Gonococci have occasionally been found; Crismore, Schüchardt, Casper, Motz and others, have reported such contaminations. As a rule the gonococci are present in the early stages and disappear in the later; they produce a gonorrhœal cystitis which renders the bladder more susceptible to tuberculosis and sometimes seems to determine the starting point of this disease in the bladder.

Location of Lesions.—In bladder tuberculosis, secondary to the kidney implication, the first evidence is seen around the orifice of the ureter; this extends either backward or upward, involving the posterior part of the trigone and the mucosa behind it. When the disease comes from the prostate, it implicates the trigone, the neck of the bladder and surrounding tissues. There are several instances to prove that a tuberculous kidney may give rise to infection only of the mucosa around the orifice of the ureter, then skip entirely the base of the bladder and infect the prostate. I have seen such a case, and Bandler and others have recorded similar observations.

In 83 cases of my series the lesions were localized as follows: In the trigone or near it, 27 times; in the orifice of the ureters or adjacent to their margins, 23 times; in the base of the bladder, by which is meant the region behind the trigone, 10 times; in the posterior wall, 7 times; in the anterior wall, 7 times; in the vesical neck, 7 times; in the superior portion of the bladder, twice.

Le Fur out of 60 cases in 12 found the lesions in the region of the ureteral openings; in 10 in the base; in 9 on the posterior wall; in 5 on the anterior wall; in 5 on the trigone; in 3 on the neck; in 3 on the neck and trigone.

Single ulcers limited to the anterior wall have been seen by Strauss and Jacquet.

Complications.—It is relatively rare for tuberculous ulcers to penetrate the bladder wall; when perforation occurs it is usually found in the base. I have observed two instances: One in the superior part of the bladder, which extended to the rectus muscle, with abscess formation; the other perforation had occurred through the trigone into the prostate.

Guon has reported a number of ulcerations through the base. Denzel found one which extended to a pocket behind the prostate. A similar instance was observed by Dittel. Muster, in a girl of 18, discovered a fistula from the bladder into the vagina. Barlow noted a communication between the posterior urethra and rectum. Lichtwitz and Ungerer record fistulous openings from a tuberculous bladder into the groin. Bovis noted a tuberculous fistula which ran from the bladder to the umbilicus; it was thought that the urachus had not entirely closed and had been made larger by the tuberculous process. Denzel observed an aperture from the bladder into the peritoneum resulting in peritonitis and death. Hewett examined a perforation of the abdominal wall between the umbilicus and symphysis and another breach in the same bladder which joined it with the rectum. Bryson, Pousson, Lane, Marchand and Schücking have seen fistulous tracts between the bladder and the rectum. Englisch noted a connection of the bladder with the small intestine. Winckel, in a study of 2505 autopsies in the female, detected 4 tuberculous ulcers which had penetrated the bladder wall.

McCabe and Clado found diverticula in two cases; in the record of the former the sac was larger than the bladder.

Phosphatic concretions have been observed over the surface of tuberculous ulcers, and well-formed stones have been repeatedly found. Bocaloglu and Gleize report an instance in which a large stone had formed in a tuberculous bladder, ulcerated through the rectum, and presented itself at the anal orifice.

ASSOCIATION OF TUBERCULOSIS OF THE BLADDER WITH THAT OF THE OTHER GENITO-URINARY ORGANS.

In 411 cases out of a collected series of 447, the involvement of the other genito-urinary organs was specifically stated. The result is as follows:

Bladder and kidney	119
Bladder and prostate	33
Bladder, prostate and epididymis	30
Bladder, kidney and prostate	28
Bladder and epididymis	26
Bladder, kidney, prostate, vesicles and epididymis	26
Bladder, kidney, prostate and epididymis	24
Bladder, prostate, vesicles and epididymis	23
Bladder, kidney, prostate and vesicles	13
Bladder, tubes and uterus	12

Bladder, kidney and epididymis	11
Bladder, vesicles and epididymis	11
Bladder, prostate and vesicles	10
Bladder, kidney, vesicles and epididymis	7
Bladder and Fallopian tubes	6
Bladder and vesicles	6
Bladder, kidney, Fallopian tubes and uterus	4
Bladder, kidney, Fallopian tubes and ovaries	2
Bladder, kidney and ovaries	2
Bladder, kidney and tubes	2
Bladder, kidney and uterus	2
Bladder, tubes and ovaries	2
Bladder, tubes, ovaries, uterus and vagina	2
Bladder, tubes and vagina	2
Bladder, kidney, Cowper's gland and urethra	1
Bladder, kidney, tubes and vagina	1
Bladder, kidney and urethra	1
Bladder, kidney and vagina	1
Bladder, kidney and vesicles	1
Bladder, ovaries, uterus and vagina	1
Bladder and uterus	1
Bladder and vagina	1

In 22 instances of bladder tuberculosis in the Johns Hopkins Hospital Pathological Laboratory, the other genito-urinary organs affected were as follows:

Bladder, kidney, (8 with ureter)	9
Bladder, kidney and epididymis	3
Bladder, kidney, prostate and epididymis	3
Bladder, kidney and prostate	3
Bladder, kidney and ovary	1
Bladder, kidney, prostate, vesicles and epididymis	1
Bladder, kidney and uterus	1
Bladder, prostate and epididymis	1

THE ASSOCIATION OF BLADDER TUBERCULOSIS WITH THAT OF OTHER SINGLE ORGANS.

Bladder and kidney	245
Bladder and prostate	187
Bladder and epididymis	158
Bladder and vesicles	97
Bladder and ureters	67
Bladder and tubes	33
Bladder and urethra (with prostate)	31
Bladder and urethra (without prostate)	7

Bladder and urethra (female)	4
Bladder and uterus	22
Bladder and vasa deferentia	19
Bladder and ovaries	9
Bladder and vagina	8
Bladder and Cowper's gland	1
Bladder and lungs	134
Bladder and bone	15
Bladder and intestine	8
Bladder and liver	5
Bladder and peritoneum	4
Bladder and spleen	4

Primary Genito-Urinary Tuberculosis.—I have searched the histories carefully in order to determine in what number the tuberculosis had originated in the genito-urinary tract. I have taken for granted, when the lungs are said to have been healthy, and no mention is made of implication of any other organs that the disease was probably primary in the genito-urinary tract. I have presumed also that this was first involved, when the chief description was confined to it and no mention was made of tuberculosis in any other part of the body. According to the above explanation, I found 145 cases in which the process seems to have commenced in the genito-urinary tract. They are as follows:

Lungs stated to be negative	39
No mention of other organs	54
Primary in genito-urinary organs (stated)	52
	145

Secondary Genito-Urinary Tuberculosis.—In 122 cases the primary focus was mentioned, but in 17 not definitely stated.

Primary in lungs	74
Primary in bone and joints	15
Primary in glands of neck	7
Primary in pleura	7
Primary in skin	2
Primary focus indefinite	17

Order of the Invasion of the Genito-Urinary Organs.—In 279 instances there were sufficient data to enable one to form an approximate idea as to the invasion. The kidney seemed to be first implicated in 184; the epididymis in 80; the prostate in 6; the fallopian tubes in 6; the seminal vesicles in 2; and the uterus in 1. In perhaps many more some portion of the genito-urinary tract was the primary seat of the tuberculosis, but the history was not given with sufficient clearness to afford certainty on this point.

From the above it is seen that the two organs from which the bladder is most frequently infected are the kidney and the epididymis, the former source supplying by far the larger number of cases. From the epididymis, the disease spreads along the vas and affects the seminal vesicles and prostate, later implicating the posterior urethra and bladder. The testicle, in contradistinction to the epididymis, is so exceptionally the primary seat of disease, that practically it need not be considered as a point of origin. In my opinion the prostate is not often primarily affected, but I would hasten to add that Koenig, Tuffier, Simmonds and Krzywicki are of the contrary opinion and hold that it frequently contains the initial focus. Heiberg in a series of 31 cases of secondary genito-urinary tuberculosis, found the process limited to the prostate in three instances; but in his primary series of 14, it was never affected alone. Krzywicki in 14 collected cases of tuberculosis of the prostate records two similar examples and Collinet has also described two.

That the vesicles may provide the genito-urinary source of origin of the disease is undoubted, but it is generally admitted that the invasion is usually secondary; a few instances of tuberculosis confined to them, however, have been observed by Oppenheim, Kocher, Orth and Dreyer.

ETIOLOGY.

The bladder is very resistant to tubercle bacilli and may withstand their continued presence for months or even years without becoming infected. This has been shown numbers of times in cases of tuberculosis of the kidney, in which the urine has been full of tubercle bacilli for months and yet the bladder has remained entirely uninfected. Experimental work also abundantly proves this point.

The bladder is rarely affected primarily; the only exception is that recorded by Saxtorph, who in 10,016 general autopsies, in a single instance found the female bladder to contain the only focus of tuberculosis in the body. Heiberg observed at autopsy a tuberculous female bladder, the remaining genito-urinary organs being free; but in this case the process was secondary to an infection in the glands of the neck.

Clinically, primary bladder tuberculosis has been reported often, but as the pathology is being more carefully studied, we are becoming convinced that these reports were erroneous. I feel justified, therefore, in saying that while primary tuberculosis of the bladder is a possibility, for practical surgical consideration its existence may be disregarded.

Tuberculosis of the lungs and of bone seem to be more frequently followed by tuberculosis of the bladder than of any other organ. In 394 autopsies which showed disease of the lungs, there were 16 instances of implication of the bladder; 13 times in connection with chronic, and 3 times with general miliary tuberculosis. In 45 cases of bone tuberculosis the bladder was affected 4 times.

Experimental Work.—I have injected virulent tubercle bacilli into the bladders of a series of rabbits under different conditions; (1) into the normal bladder, (2) into that organ after having curetted the mucous membrane; in neither series have I been able to produce an infection. I have this work still in progress and will give a full report later.

Hanau introduced tubercle bacilli into the urethra of guinea-pigs and succeeded in inducing tuberculosis of the urethra and bladder.

Rovsing has demonstrated that tuberculosis of the bladder cannot be produced by injecting tubercle bacilli into it, even if they be allowed to remain 24 hours, but he did succeed after contusing the mucous membrane and keeping the organisms imprisoned for 20 hours.

Baumgarten caused a tuberculosis of the posterior urethra, prostate and neck of the bladder in rabbits, by instilling the bacilli deeply into the urethra.

Hansen, in 16 cases of artificial tuberculosis of the kidney, had two in which infection of the bladder subsequently developed. In 7 other animals, he injured the mucous membrane of the bladder very extensively, and then injected tubercle bacilli; 4 of these experiments gave positive results.

Pyogenic Organisms.—It is impossible to state the exact influence which pyogenic cystitis exerts upon the infection from tubercle bacilli, but it is probable that such an inflammation lowers the resistance of the mucosa, and produces minute breaks in the surface, which allow the tubercle bacilli to enter the submucosa. On the other hand, the increased blood supply and the extensive infiltration of leukocytes and lymphoid cells, together with a possible inhibiting influence of the toxins of certain pyogenic bacteria, may offer definite resistance to the tuberculous invasion.

The inhibition of pyogenic toxins just mentioned has not been proved and may not exist at all, for we see many specimens from kidneys, bladders, intestines and other organs in which pyogenic bacteria and tubercle bacilli have grown together on apparently very friendly terms. Nevertheless, it would seem that a cystitis caused by members of the proteus group or certain varieties of the colon bacilli does not offer so fertile a field for the invasion of tubercle bacilli as that produced by streptococci and gonococci. These last two organisms unquestionably are good forerunners for tuberculosis.

It can be stated, however, that in no case of cystitis, be it ever so bad, does the bladder ever become infected with tubercle bacilli even if tuberculosis of the lungs, bone or other part, exists, unless some other portion of the genito-urinary tract is implicated.

In this connection it must be insisted that all patients who have any focus of tuberculosis in the genito-urinary organs should be protected as far as possible from anything which might give rise to a cystitis, and that when such does occur it should receive more than ordinarily careful treatment.

Gonococci.—The question as to the predisposing influence of gonorrhœal inflammation is not definitely decided, but in view of the fact that a number of cases of bladder tuberculosis have followed closely upon acute gonorrhœal urethritis and cystitis, it would seem highly probable that an attack of gonorrhœa occurring in individuals suffering from tuberculosis of the kidneys or epididymes may favor the development of a bladder tuberculosis. It must be stated, however, that about 85 per cent. of adult males, and a fairly large proportion of adult females, have had a gonorrhœa at some time during their lives, so that the relationship is possibly more co-incidental than real.

In 135 cases of my collected series, gonorrhœa was stated to have been present in 71 and denied in 64. In a few the tuberculosis followed the acute attack, but in most of them it was remote.

Casper saw two instances of bladder tuberculosis develop immediately after an attack of acute gonorrhœa; so far as he could discover there had been no tuberculous focus in the body before and Casper thought that the tubercle bacilli had been directly implanted on the injured mucosa. How they gained entrance he does not state. Such a conclusion is certainly open to question.

Cornil, Babès, Motz, Hallé and Bloodgood have found gonococci and tubercle bacilli associated in the urine. Routier and Holländer have reported a cystitis which followed an acute gonorrhœa and which later was proved to be tuberculous.

Loomis, in a patient who had had for some time a cough and occasional pain in the region of the kidney, observed frequent and painful micturition following an acute gonorrhœa; the process proved to be tuberculous and ran a rapidly fatal course. It is probable that the patient had a primary disease of the kidney and that the gonorrhœa caused the bladder to become affected, thus increasing the rapidity of the whole process.

Sexual Intercourse.—It is possible that either the male or the female may become infected during coitus, but such an occurrence is extremely rare, and the few instances which have been reported are open to doubt. If such an infection does occur, it is more likely to happen to the female, the tuberculous semen being deposited in the vagina and remaining for several days in contact with the cervix or making its way into the uterus.

Greize reports the case of a male of 37, who was thought to have been infected by a woman suffering from tuberculosis of the cervix. Gracienescu mentions the case of a female who, after cohabitation with a man suffering from local tuberculosis, developed the disease.

Schüchardt believes in the danger, and has observed a tuberculous ulcer develop on the glans penis after intercourse. In another instance he examined a female who had a very severe and acute inflammation of the vagina, the secretions from which showed gonococci and tubercle bacilli; this condition had developed after intercourse with a tuberculous male. In this connection, it is interesting to note that tubercle bacilli have been found, by Jani and Nakarai, in normal prostates and testicles of individuals suffering from pulmonary tuberculosis. The virulence of these bacilli was proved by Nakari, who inoculated them into animals. The germs may thus be present in the semen, in the absence of lesions of the genital organs, but these organisms must of necessity be few and can play no role as infective agents.

Instrumentation.—In individuals suffering from tuberculosis of the kidney, prostate or epididymis, the insertion of metal instruments, or stiff catheters, may wound the vesical neck or bladder mucosa, and afford a starting point for a bladder tuberculosis. It behooves us, therefore, in all cases of this kind to limit their introduction and, when indispensable, to practise the procedure only with extreme care and delicacy.

Means of Infection.—Theoretically the bladder may become infected by the blood or lymph, but since it is so rarely involved alone and since even in general miliary tuberculosis miliary tubercles in the bladder are very seldom found, much doubt is thrown upon the occurrence of infection through these channels.

A case occurring in the Johns Hopkins Hospital, in which some of the physicians thought that implication of the bladder had occurred in this way, may be cited as an example. The patient had had no bladder disturbance, nor change of urine during life; at the autopsy there were discovered two gray tubercles (miliary) in the trigone, and a few in both kidneys, the other genito-urinary organs being free. Here there is a possibility, of course, that the tubercle bacilli may have been conveyed to the bladder by the blood or lymph; but on the other hand, they most certainly could have come down from the kidneys.

The two principal modes of infection then, are: First, from the kidney above, and second, from the epididymes, prostate and vesicles below. The tubercle bacilli from the kidney enter the bladder in two ways: (1) They may pass by direct extension from the mucous membrane of the ureter to that of the bladder; (2) they may be brought down in the urine, and enter the submucosa through some microscopic fissure. From the prostate below, they either enter by direct invasion through the base of the bladder, or implicate first the prostatic urethra and then the bladder mucosa.

Extension from the peritoneum directly through the bladder wall is spoken of as a possibility, but there are no undoubted observations to confirm it. I have been unable to find any evidence of such a penetration in the specimens which I have examined.

It is thought to be possible by some observers that the disease may extend from the rectum into the bladder; such an occurrence I have found neither in the literature nor in my personal experience.

Traumatism.—Trauma of one kind or another may prove a predisposing factor, but there are no recorded instances to substantiate this opinion.

Diseases of the Urethra.—In cases of genito-urinary tuberculosis, inflammatory thickening, particularly when it gives rise to the formation of stricture, seems to be a predisposing factor in inciting the development of bladder tuberculosis.

Crismore, Motz, Hallé, and others have reported instances in which the stricture had a very baneful influence. Jamin observed a lighting up of a very severe cystitis, presumably tuberculous, after dilatation of a urethral stricture.

Stone has been found not infrequently associated with bladder tuberculosis. In some subjects it has preceded the development of the disease several years. Bacaloglu and Gleize report the case of a patient who had suffered a long time from attacks of cystitis which alternated with periods of improvement; these attacks gradually became worse, and at the operation a stone the size of a pigeon's egg, weighing 25 grammes, was removed; some time later tubercle bacilli were discovered in the urine, and tuberculosis of the epididymes and prostate developed.

Carleton observed a man who had complained for a long time of symptoms of bladder stone. At the operation a large calculus was found and the bladder mucous membrane was tuberculous.

In the Johns Hopkins Hospital there were about thirty small stones removed from a tuberculous bladder; calculi continued to form for several months and were taken out from time to time.

Heredity.—There were 100 cases in which were recorded notes as to the presence or absence of tuberculosis in the family; 55 patients acknowledged that some member had suffered from the disease, 45 denied it. It is probable that the hereditary tendency (as now understood) plays the same part in tuberculosis of the genito-urinary organs as it does in other parts of the body.

Habits.—The records were not full enough for me to determine whether the use of alcohol, excessive sexual indulgence, and other forms of dissipation acted as predisposing agents; my own opinion, however, is that a virtuous life does not materially lessen the chances of infection of these organs by tuberculosis.

Professions, Trades, Etc.—Accurate statistics in regard to this point were not forthcoming, but I feel sure that the larger proportion of cases of genito-urinary tuberculosis will be found among laborers and those who have been compelled to lead lives of exposure and hardship.

Sex.—Of 438 patients of whom the sex was given, there were 285 males and 153 females. The statement of some observers that the disease is quite as common in females as in males—perhaps even more common—must certainly be incorrect, because in the male there are additional sources of infection—epididymes, prostate, vesicles, to which in the female there are no organs that are analogous in this connection. Indeed, in the female the kidney is practically the only source of infection. In order, however, to be entirely just, I will state that in this study I have been particularly interested in male tuberculosis and possibly may unintentionally have overlooked some females.

Age.—The youngest patient (condition found at autopsy) was a child of two years (Peroud); the oldest was a man of 97 (Tapret). Ammond's patient was a child of 3½ years; Horwitz's 3 years; West's 4 years; Moullin had one of 4 years, and a man of 70 years of age. The age according to decades is as follows:

IN THE MALE:		IN THE FEMALE:	
1 to 10	4	1 to 10	2
11 to 20	32	11 to 20	20
21 to 30	94	21 to 30	37
31 to 40	70	31 to 40	26
41 to 50	50	41 to 50	11
51 to 60	14	51 to 60	2
61 to 70	6	61 to 70	5
71 to 80	0	71 to 80	1
81 to 90	0	81 to 90	0
91 to 100	1	91 to 100	0
	271		104

The average age in females as obtained from 104 cases is 37.78 years; the average age in males in 271 cases is 33.26 years.

SYMPTOMATOLOGY AND DIAGNOSTIC DATA.

There is no one sign nor symptom, nor is there a definite symptom-complex which indubitably proves the presence of tuberculosis of the bladder. Direct inspection only can justify an absolute diagnosis. The same frequent and painful micturition and the general bladder distress which accompanies tuberculosis of that organ is also produced to nearly the same degree of intensity by tuberculosis of the kidney, and almost the same symptomatic picture is presented by certain cases of tuberculosis of the prostate. This fact has been proved often by autopsies and cystoscopic examinations. A very interesting example has been recorded by Keys, in which a patient was compelled to urinate every 5 or 10 minutes, and yet at autopsy there was disclosed no implication of the bladder.

The localized symptoms most generally met with are frequent and painful micturition, a dull aching sensation in the pelvis, and the presence of pus, tubercle bacilli and blood in the urine. The general symptoms are a gradual loss of flesh, an increasing anæmia, an irregular temperature, occasional chills, etc.

It should be stated, however, that tuberculosis of the bladder rarely presents a picture entirely due to the disease of that viscus, for the reason that some one or the other genito-urinary organs is generally implicated.

Frequency and pain with micturition will be discussed first together, because they are so often associated, and then singly.

In 294 reports in which the symptoms were given, there were 201 which gave this as a prominent complaint in some stage of the disease. In a number of others, it was not specifically stated that pain and frequency of micturition were met with together, but from other signs present, it is presumable that such was the case; if such cases are added to the above list, the proportion would be much larger, so that I do not think I should err in saying that over 95 per cent. present the combination of frequency and pain with micturition. This complex sometimes occurs at intervals, remains for a few days or even several weeks, and then passes off almost entirely for a variable period, such free intervals and recrudescences covering several years. This type is exceptional, the general rule is a steadily downward progress, the pain becoming greater and micturition more frequent.

As an example of the above, one of my patients twelve years ago had an attack of cystitis (with frequent and painful micturition), which lasted for three days; this entirely disappeared and there was no further trouble for three years, when a second attack occurred. This was soon followed by others, and after a while the intervals became shorter and shorter until finally the suffering became continuous.

Frequency of Micturition.—In the very beginning, there is an augmentation in the quantity passed, but no change in the frequency of urination. Soon there is noted an increase in the number of times during the day, and the patient, who has before slept all night, is now forced to get up once or twice. This frequency gradually increases as the disease progresses and is accompanied by burning and pain. The intervals become shorter and shorter, the average in the later stages being from 20 to 30 minutes; in the more extreme cases, micturition occurs every 5 to 10 minutes during the day and night. Basset and Perkins observed a case in which the patient passed water every 5 minutes; Routier recorded an instance of 40 micturitions during the day and the same number during the night. One of my patients had 27 calls during the daytime. In women it is sometimes necessary to wear a napkin.

This symptom is neither relieved by rest nor increased by exercise, nor is it diminished to any extent at night. The underlying cause of frequent urination in bladder tuberculosis is the irritation of the vesical neck and floor of the prostatic urethra by the morbid process. This renders the nerve endings which normally control the phenomenon of micturition much more easily impressed; consequently the bladder becomes intolerant of much fluid. In the bladders which show an implication of the superior half, with a comparatively free base, frequent micturition is not prominent.

Pain.—At the very first pain is usually absent. As the disease advances, it becomes more and more in evidence, and toward the last stage is sometimes intolerable; it is described as dull, aching, occasionally sharp or lancinating; it is felt at the beginning of, during, or at the end of micturition; most frequently, however, pain accompanies the whole act, with an exacerbation at the end. It may be transmitted all along the urethra, or confined to the prostatic portion, and in a few patients it is felt only in the glans penis. After micturition it continues for several minutes, but is not acute, the patients describing it as a dragging, burning sensation. It is usually associated with frequency, but to this there are a few exceptions. In two cases in the Johns Hopkins Hospital, there was marked frequency but no pain. Guyon and others have noted similar instances. In a few the pain was the initial symptom and remained for some time before any other bladder disturbance was noted. It is transmitted occasionally to the perineum, to the suprapubic region, down the legs, and to the renal region; sometimes the pain is continuously present and is of a very sharp neuralgic type, extending over the whole back.

The pain is produced by the ulceration and tuberculous process in and near the vesical neck, and is intensified by the contraction of the bladder during and after micturition. When only the superior half of the organ is affected the pain is very much less and may be altogether absent.

Changes in the Urine.—It is difficult to state the exact alterations in the urine caused by bladder tuberculosis, for the reason that this process is usually complicated by tuberculosis of the kidney or prostate. Given then, an unusual condition in which the bladder has become infected from the epididymes, prostate, or vesicles, and where the focus does not communicate with the urethra, the very first change would be an increased secretion of urine due to excitation of the kidneys. Following very soon upon this augmentation in the urine, pus and exfoliated bladder epithelial cells appear, along with a few red corpuscles and possibly some tubercle bacilli. As the disease advances the pus becomes much greater in quantity, the blood is more in evidence, and the tubercle bacilli are more readily demonstrated. Still later, in the stage of ulceration, there is added to the above debris consisting of necrotic and cheesy material.

The reaction in the majority of urines is acid: in 46 recorded analyses, 28 urines were acid, 14 were alkaline, 3 were ammoniacal, and 1 was neutral. The average specific gravity was 1018; the lowest was 1006, and the highest was 1022. The urea varied from 8 to 13 grammes per litre. The prosphoric acid (P_2O_5) ranged about 0.65. The chlorides, according to a late investigation by Bignon are usually increased, particularly when the kidney is involved. There is no reason for any alteration of the chemical constituents of the urine in tuberculosis of the bladder except as a result of reflex stimulation of the kidney; the real deviation from normal in this respect is induced by disease of the kidney.

Blood.—Hæmaturia is not so infrequently the first symptom, and may be present at intervals for a number of years, before any bladder distress or other signs show themselves.

In 146 cases bleeding was noted at some stage of the disease, in 20 it was an initial symptom. There is no absolutely characteristic sign which under all conditions will enable us to differentiate between blood from the kidney and blood from the bladder, except the evidence of cystoscopic examination. Usually the blood coming with the last portion of urine, or at the end of micturition, signifies that either the bladder or vesical neck is its source; homogenous red urine may indicate bleeding either from the bladder or kidney; if it comes from the bladder it means that there is an extensive process of some kind present; if this can be reasonably excluded, the bleeding is presumably renal in origin.

The periods of bleeding vary in duration from a few hours to several weeks and occur at intervals of weeks, months, or even years; they are most frequently met with in the first stage of the disease and tend to diminish toward the end; the quantity of blood lost, as a rule, is small; sometimes, however, it is large, and exceptionally it has been sufficient to endanger life.

Clado observed a patient who bled continuously for 1½ years. Pierchon cites an initial symptom of profuse bleeding which was prolonged for several weeks. Raymond had a patient who suffered from bleeding at intervals for 7 years before bladder distress developed. Casper's patient had had hæmaturia for 5 years prior to the appearance of any other sign of tuberculosis. In one of Raillaird's cases there was paroxysmal hæmaturia for eighteen years; in one of Talayrach's for three years. Horwitz observed one case in which bleeding occurred at intervals for three years before the cystitis began. These were all probably instances of primary renal tuberculosis.

The hæmaturia is caused in two ways. First, in the earlier stages, when there is much congestion and some ulceration, the blood is squeezed out by the contractions of the bladder; secondly, later when the ulceration is more extensive, the blood vessels may become eroded and the blood be poured out in larger quantity.

Tubercle Bacilli.—These organisms were frequently reported as absent; this I take to be the result of inadequate examinations, for a careful search will always reveal them. They were recorded as present in 110 cases—in a little over 50 per cent. of the histories in which the results of an examination were given.

The presence of tubercle bacilli in the urine does not always mean that tuberculous lesions are present in the bladder, for it has been proved that they may be excreted by the kidney and appear in the urine in the absence of any disease of the urinary tract. Israel on two occasions found them in the urine of a patient who at autopsy showed a complete absence of genito-urinary tuberculosis. Thiliewicz disclosed their presence in the urine in a case of miliary tuberculosis which at autopsy showed no local lesions. The observations of Jani and Nakarai have already been mentioned.

Pyogenic Organisms.—The most common secondary bacteria present in the urine, as before stated, are colon bacilli, diplococci, streptococci, and members of the proteus group.

These, particularly colon bacilli, are usually present in the terminal stages. Members of the proteus group are seen in the ammoniacal and occasionally in other alkaline urines. Gonococci have been demonstrated a few times.

The total quantity of urine passed in the twenty-four hours varies with each individual case, but is liable to be somewhat above normal. The smallest quantity, 800 cc., was observed by Battle in a ten-year-old girl; the largest amount, 2500 cc., occurred in a male of 47 (Bignon); the average quantity was 1660 cc. Sondern in 74 cases found the average to be 1430; the largest was 2200 cc. and the smallest was 720 cc.

The capacity of the bladder is diminished. This as demonstrated in 41 cases averaged 97 cc.; the smallest was 20 cc. (Catron) and the largest was 420 cc.; of these 41 bladders, 27 had a capacity of under 100 cc.

Cystoscopic Examination.—In the bladders which have been infected from the kidney, we see on the corresponding side on cystoscopic inspection an irregular ureteral orifice with some swelling and redness on the edges and a slight congestion of the surrounding mucous membrane, with the occasional presence of a few reddish papules. This picture does not represent a true tuberculosis, but is rather that of irritation produced by the tuberculous toxins. Later there is seen an increase in the red zone and the formation of definite tubercles which appear as fine gray points with a faint reddish zone surrounding them. In a short time this picture is succeeded by another, which shows a development of more tubercles, with an aggregation, coalescence, and secondary loss of substance, and the consequent formation of one or more minute ulcers. The mucous membrane in this stage is otherwise normal, except for a slight congestion in the trigone and vesical neck. A still later examination discloses an extension of the ulceration toward the trigone, or upward and backward on the posterior and lateral surfaces. Following this increased ulceration, the whole mucosa not infrequently becomes injected and slightly swollen, and presents the picture of a cystitis; this is particularly true when there has been a secondary invasion. In the last stages there is a very extensive ulceration of most of the mucous membrane and in many places an exposure of the muscular coat.

When the disease comes up from the prostate, nearly the same picture is presented with the exception of the above mentioned initial and probably non-tuberculous stage; the lesions, of course, are differently located, being near the vesical neck and in the trigone. In this type there seems to be a more rapid development of tubercles, with an earlier breaking down and ulceration, the more rapid course being probably due to the situation of the lesions which are thus subjected to more irritation from the contractions of the bladder.

Tuberculous Ulcer.—The outline is irregular; there is a general tendency toward a circular form with irregular projections; the edges are ragged, red, swollen, slightly indurated, and overhanging; the base is covered with an uneven, very delicate granulation tissue, over which are scattered yellow and gray flakes of fibrin. The mucous membrane immediately surrounding the ulcer is diffusely reddened and no individual blood vessels can be seen; outside of this is a less reddened zone, where they are more distinct. The ulcer varies in depth; usually it does not penetrate farther than the submucosa tissue, but occasionally it passes through this and exposes the muscle, which in turn it erodes.

According to descriptions found in the literature, the ulceration in a majority of instances begins in the region of the ureter; the individual ulcers range in size from that of a pin-head up to that of a silver dollar; usually several are present, but single ones have been noted by Strauss, Reynès and Battle.

Unusual Conditions.—Stoeckel observed a bladder whose base was covered with polypoid excrescences; these were very small, and for the most part were translucent; some of them were slightly reddened; there were no tubercles, no ulcers; tubercle bacilli were not found at first, but were discovered later. Mirabeau has made a similar observation in a case which also proved to be tuberculous.

Malherbe saw a brownish mass which at first was taken for a tumor, but later at operation was shown to be a tuberculous process.

Incontinence.—Three kinds of incontinence are met with: (1) The true form which is brought about by the destruction of the vesical neck; (2) that of dribbling from over-distention; (3) that caused by an exaggerated and imperious desire to micturate. True incontinence is observed only in the last stages, when the disease has become extensive, infiltrative and destructive. The over-distention type is produced either by some obstruction in the prostatic region, or by grave implication of the muscle which weakens it and allows the bladder to distend. In the last form the urine begins to flow as soon as the desire is felt.

Retention of urine is sometimes seen. It occasionally appears very early, and the first thing that draws the attention of the patient to any abnormal state is that he suddenly becomes unable to urinate and is compelled to have recourse to a catheter. Retention is brought about in four ways: (1) By irritation around the vesical neck which produces a spasmodic constriction; (2) by the implication of the prostate or the swelling of the tissues around the neck of the bladder which forms an obstruction; (3) by hindrance of the outflow by a blood-clot; (4) by more or less complete destruction of the muscle wall of the bladder which so weakens it that the viscus has not sufficient force to expel the urine.

Tuberculosis of the Bladder Without Symptoms During Life.—Every now and then one finds at autopsy a more or less extensive disease of the bladder which has produced no symptoms before death. In such instances it is usually the superior half of the viscus which has been invaded.

Stein saw at autopsy a number of ulcerations at the summit of the bladder, the patient having complained of no disturbance of micturition. Kidd observed a very extensive ulceration of the mucous membrane, which had caused no bladder distress. Smith saw a single ulcer which was not known to have caused any discomfort before death. In three patients in the Johns Hopkins Hospital there had been no trouble with the bladder, but at autopsy lesions were found; in the first there was a decided implication of the mucous membrane; in the other two there were several fine gray tubercles in the trigone.

Loss of Flesh.—In the early stages of bladder tuberculosis, the patient retains his weight to a remarkable degree and occasionally gains from time to time; it is the rule, however, in the latter half to have loss of flesh, which in the terminal stages becomes rapid. This cannot all be ascribed to the disease of the bladder, for there are other tuberculous foci present which are preying upon the patient. Again, the emaciation is in part directly due to exhaustion and loss of sleep, caused by the frequent and painful micturition.

Anæmia.—A certain degree of pallor is observed very early, although some persons retain their color for a long time; later the anæmia is very pronounced and the blood presents the same changes as in tuberculosis of other organs.

Fever.—This is a late symptom, is of irregular type and ranges from 99° to 103° F. Chilly sensations and occasionally definite rigors precede the rise in temperature.

Pulse.—The pulse sympathizes with the general weakness and the temperature.

Complications.—The main complications are infection by pyogenic organisms, stone, stricture, and prostatic abscess. Secondarily, of course, we may have those following perforation of the ulcer into the surrounding structures. Infection by pyogenic bacteria and the presence of stone have been discussed already. Stricture has been observed several times in this connection, and often aggravates the other symptoms and increases the rapidity of the course of the disease. Typical instances have been recorded by Motz, Crismore, and others. Prostatic abscess often complicates tuberculosis of the bladder; it produces retention, great increase in the pain, local swelling and discomfort in the perineum. Perforation into the large or small intestine, may allow all the water to be discharged into the bowel, greatly increases the suffering, and hastens the end. Perforation into the peritoneum produces peritonitis and death. Opening into the perineum, behind the prostate, or into the suprapubic region gives rise to abscess formation with its consequent train of symptoms.

Duration of Symptoms.—Inasmuch as bladder tuberculosis in every instance is complicated by other conditions, such as tuberculosis of the kidney or prostate, primary stone and primary simple cystitis, it is impossible to state with precision how long tuberculosis of the bladder had been present in the cases which I have analyzed. In the following calculation I have estimated the time from the date of the first symptoms up to the time at which the patient first came under the observation of the recorder of the case. This method must of necessity be inaccurate, for the records are indefinite—for instance, the following phrases are used: "Blood at intervals for 5 years, later painful and frequent micturition;" "Cystitis to some extent for 10 years, several years later increased frequency with pain;" "Symptoms of stone for 4 years; then tuberculosis developed." Such cases may or may not have been tuberculous from the beginning; possibly in some the process at first was simple and a tuberculous infection occurred only later. With the above explanation, I will state that I have computed the time in 172 cases, and find that the average duration of the bladder tuberculosis from the beginning up to the date of the history is 25.21 months. The shortest time was 14 days and the longest 11 years. The duration of symptoms from the beginning to the time of death, as calculated from the histories in which the dates were given, is 35.05 months, or in round numbers 3 years.

(To be continued.)